

Fertile Hopes

Fertility-sparing therapies and assisted reproduction have increased the odds of conception after cancer

By Sue Rochman

Gail Murray had always wanted a child. So when the San Francisco Bay–area resident learned at age 38 that she had endometrial cancer and required a hysterectomy, her world caved in. “I cried harder over that than knowing I had cancer,” she says. “I wanted a family so badly and that was being taken from me.”

To keep hope alive, Murray (with her doctor’s blessing) delayed surgery for 30 days—just enough time to undergo in vitro fertilization (IVF), an assisted reproductive technique that would leave her with embryos for the future. First Murray had to inject herself with hormones that would stimulate her ovaries to produce a large number of eggs. Then the eggs were surgically removed and fertilized in a petri dish with her partner’s sperm to create a number of embryos, which were ultimately frozen. As a result, Murray went into cancer surgery knowing that although she would no longer be able to become pregnant herself, one of the frozen embryos could be implanted in a surrogate womb, giving her the chance to have a family.

Women with gynecologic or breast cancer must not only face their diagnoses, but also the possibility that cancer treatment may affect their ability to have a child. Chemotherapy itself destroys a fraction of the eggs a woman has in reserve, pushing her closer to menopause. For those with gynecologic cancer, treatment could require removal of the ovaries or uterus, preventing conception or the ability to bear a child at all. Radiation to the pelvic area damages ovaries and eggs.

In years past, potential loss of fertility was something breast and gynecologic cancer patients were asked to simply accept. Compared to beating the cancer, doctors told them, concerns about fertility took a distant second place. But today, with more cancer patients surviving and more women than ever having children later in life, the situation has changed. In response to demand from patients, a host of new and refined fertility techniques geared specifically to cancer survivors now significantly increase their odds of having biological children of their own. From IVF therapies modified specifically for breast cancer patients to surgery that preserves reproductive organs, a new specialty in fertility-preserving oncology has come of age. Many of the procedures are still experimental, and some can be expensive. There are no guarantees. But many women are finding that if fertility concerns are integrated into cancer treatment from the start, they may dramatically extend their fertile years and go on to conceive.

The Rise in Fertility Consciousness

The most important step in preserving fertility despite cancer treatment, of course, is integrating that goal into your treatment plan from the start. Yet a few short years ago, this was a daunting task. It was in 2001 that a young tongue cancer patient named Lindsay Nohr Beck, then 24, was told the chemotherapy she required could threaten her fertility, but was offered no real options to deal with the risk. “While my vast team of extraordinary doctors was empathetic toward my situation, their priority was clear—survival,” says Beck. Instead of fertility solutions, her doctors gave her only referrals to other doctors. But these doctors too seemed unaware of fertility-preserving strategies for cancer patients.

In an impressive feat of investigation and self-advocacy for someone so sick and so young, Beck began questioning leaders in the field, calling fertility clinics and scouring Internet

sites. Without a partner, she did not want embryos created with donor sperm. Instead, she hoped to freeze just her eggs, leaving them available for a partner she might find in the future. But that technology was experimental. Finally she lucked out: After several calls to Stanford Medical Center, a woman on the other end of the line told her that they did indeed have a program for freezing unfertilized eggs through a technique known as “oocyte cryopreservation,” available only for cancer patients. “It was the first time in my life I was happy to be a cancer patient,” Beck says.

Not long after, Beck founded the nonprofit organization Fertile Hope, devoted to helping cancer patients preserve their fertility. The need for the group was clear: Up to 90 percent of young people undergoing cancer treatment become infertile as a result, but only half are informed of the risk, let alone given alternatives. Joining forces with other activists and a few pioneering physicians, Fertile Hope set out to raise consciousness and promote fertility-preserving techniques.

No matter what the cancer, says Fertile Hope, the questions a patient must ask at the outset of treatment are much the same: Will the proposed treatment impact the reproductive system? If so, how? What alternative treatments might offer more protection? What can be done to help preserve fertility prior to treatment? Can doctors monitor treatment for fertility risk and change course if necessary? If infertility results, what options remain?

End-Run Around Chemo

No matter what form of cancer, one serious threat to fertility often is chemotherapy, which targets not just cancer cells but healthy cells, too. According to reproductive endocrinologist Kutluk Oktay, M.D. of the Weill Medical College of Cornell University in New York and a leading expert in preservation of fertility for cancer patients, “women are born with all of the eggs they will ever have, about a million of them, and use that reserve of eggs until they run out; that’s when menopause is typically initiated. Chemotherapy accelerates this process. With each course of chemotherapy, a certain fraction of the eggs are lost.” Once chemotherapy is finished, the patient’s fertility timeline will be shorter than before, but whether or not the treatment pushes her into menopause depends on how old she was in the first place.

This explains why chemo is increasingly more likely to cause infertility as a patient advances in age. If a course of treatment causes ovaries to age perhaps a decade, then a woman in her early twenties might still have plenty of capacity, but one in her thirties—now with ovaries that behave as if they are in their forties—would naturally have less reserve and commensurately more trouble in attempts to conceive.

This problem can be especially great for breast cancer patients with estrogen-sensitive tumors, who are generally placed on a five-year course of the synthetic hormone, tamoxifen. Tamoxifen blocks estrogen, preventing it from stimulating the tumor, but it may also cause birth defects if used during pregnancy.

In short, tamoxifen and pregnancy don’t mix. By the time the thirty-something breast cancer patient has been sufficiently treated and can consider conception, she may be well into her forties, a time when many healthy women can have trouble conceiving anyway, Oktay says.

In light of this, women focused on fertility must make sure their doctors review the infertility risk associated with each type of chemotherapy and choose their treatments, in part, based on that. According to oncologist Ann H. Partridge, M.D. of the Dana-Farber Cancer Institute in Boston, a few recent studies comparing breast cancer chemotherapies point the way. One study compared AC (doxorubicin and cyclophosphamide) to CMF

(cyclophosphamide, methotrexate and 5-fluorouracil). The results, says Partridge, are unequivocal: CMF is associated with greater risk than AC that menstruation will stop, a situation often associated with infertility.

"Where CMF and AC are considered fairly equivalent as far as the effectiveness of breast cancer treatment," according to Partridge, "any woman who is concerned about the future of her fertility should not take a course of CMF."

Fertility-Sparing Surgery

For breast cancer patients chemotherapy is the major risk to fertility since other treatments, particularly surgery and radiation, don't typically have an impact on the ovaries or reproductive organs. But for those with gynecologic cancers, radiation and surgery can pose enormous fertility risk. Ovarian and endometrial cancer (cancer in the lining of the uterus), for instance, are usually treated by removing the uterus and ovaries completely. Only after all the cancer has been surgically removed will radiation and chemo follow to mop up.

In the early stages of these cancers, however, patients may decide to request special "fertility-sparing" procedures that remove the cancer but keep the reproductive system intact. For instance, if endometrial cancer is caught very early (75 percent of women with the most common type of endometrial cancer receive a diagnosis in the earliest stages of the disease) they may be able to preserve their ability to become pregnant by using progestin therapy instead of having surgery. In later stages of the disease, fertility-sparing surgery might remove the uterus but leave ovaries untouched, allowing doctors to harvest eggs and conduct in vitro fertilization at a later date. All this is important news for the 25 percent of those diagnosed with endometrial cancer under the age of 50. Likewise, for those with early-stage ovarian cancer, fertility-sparing surgery can mean removing just one ovary, leaving the other one available as a source of eggs.

Betsy Gasior, the current president and founder of the Greater Minnesota Division of the National Ovarian Cancer Coalition and a beneficiary of fertility-sparing surgery, was diagnosed with stage I germ cell ovarian cancer in October 1990 at age 17. "At that time," she recalls, "fertility-sparing surgery was considered radical." But she was fortunate to have found a gynecologic oncologist who believed that surgical removal of one ovary and fallopian tube followed by chemotherapy offered the best chance for a cure—and children. He was right. Five years after her surgery, Gasior gave birth to a baby boy. Her second son was born three years later.

Cervical cancer, until recently treated through radical hysterectomy, is the last of the gynecological cancers to yield to fertility-sparing surgery in the form of a new technique called "radical vaginal trachelectomy." Yukio Sonoda, M.D., a Memorial Sloan-Kettering surgeon who performs the surgery, says it involves removal of most of the cervix and tumor through the vagina. During the procedure, the surgeon re-attaches the vaginal tissue to a small portion of the cervix that is left behind. The remaining cervical stump still has an opening, which allows menstruation to occur and conception to take place.

Women with advanced gynecological cancers requiring radiation to the pelvic area, meanwhile, may be able to preserve their fertility through a procedure called "ovarian transposition." The technique, explains cancer fertility specialist Lynn Westphal, M.D. of Stanford University Medical Center, involves transplanting the ovary to an area distant from the site of radiation, either further up in the abdomen or, less often, immediately below the skin in the forearm. Whether the ovary is returned to the pelvis or stays in its new location, it can be harvested for eggs in the future—provided that the transplanted ovary starts to function normally, something that happens about half the time, Westphal warns.

The most important step in obtaining fertility-sparing surgery for a qualified candidate could be asking for it. Whether a woman is offered fertility-sparing surgery can depend as much on who her physician is as it does the type of gynecologic cancer that she has. "All too frequently the problem is that a patient sees a physician who is not up to date on what all the options are," says gynecologic oncologist David Gershenson, M.D. of the University of Texas M.D. Anderson Cancer Center in Houston. "I've seen patients who had both their ovaries and uterus removed and in retrospect they could have had fertility-sparing surgery, but their surgeon didn't understand that."

Assisted Reproduction

While the goal is preservation of the reproductive system, sometimes that is impossible. When too much has been lost, the next step is assisted reproductive technology, or ART, defined as fertility treatments in which eggs and sperm are handled together in the lab. ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman—a surrogate—to carry a baby to term. For cancer patients like Gail Murray, the ability to freeze embryos or eggs for later use has made all the difference in the world. But because these women are not just fertility patients but also cancer patients, assisted reproduction has had to be modified just for them.

Cornell's Oktay believes that conventional ART presents a dilemma for the majority of breast cancer patients, whose tumors are fueled by estrogen. The reason is clear: Normally the ovaries produce a single mature egg each month. But to capitalize on the surgical harvesting procedure, reproductive specialists typically prime the ovaries with estrogen-boosting fertility drugs, stimulating many mature eggs and making the process more efficient. But increased estrogen is a risk for many breast cancer patients, Oktay feels. As a result, he says, "many breast cancer patients underwent in vitro fertilization without stimulation, without drugs, and that meant trying to collect the one egg that the ovary creates each month." Oktay's research showed half the time these patients produced no usable eggs at all. Without ovarian stimulation, the process was often an exercise in futility and frustration.

In response, Oktay and his team studied two breast cancer drugs, tamoxifen and Femara (letrozole), both also used to promote fertility in the past. The researchers found that, using these drugs, they could boost fertility without increasing the risk of a cancer recurrence. With the initiation of the estrogen-free fertility treatments, breast cancer patients actually have an advantage over women with many other forms of cancer. The reason is the typical six-week gap breast cancer patients often have between surgery and chemotherapy, allowing enough time for doctors to stimulate their ovaries and harvest their eggs.

Once the ovaries have been stimulated and the eggs harvested, the most common scenario, IVF, involves mixing eggs with sperm in a petri dish, creating embryos that can be frozen for later use. It worked well for Gail Murray. Two years after she had a hysterectomy to treat her endometrial cancer, she and her husband decided it was time to start their family. Their frozen embryos thawed well, and, thanks to their 25-year-old niece, who volunteered to carry the baby to term as a surrogate, Murray celebrated five years of being cancer-free with her son, William, by her side.

For Lindsay Nohr Beck of Fertile Hope, on the other hand, eggs were frozen without fertilization by sperm. The innovative technique, oocyte cryo-preservation, was pioneered by reproductive endocrinologist and cancer fertility specialist Lynn Westphal of Stanford for cancer patients. "It is an option for those who don't have a partner or are uncomfortable using donor sperm. It may also be a preferred technique for women who do have a husband but don't like the idea of having embryos stored, often for religious reasons,"

Westphal says. Although the technique is continually being refined, pregnancy rates are still higher with frozen embryos than with frozen eggs.

A third technique, ovarian tissue freezing, has been pioneered by Oktay's team at Cornell. "In this procedure, the ovaries or a piece of an ovary are removed and frozen before cancer treatment that might result in infertility," he explains. "In the future, when the patient desires to get pregnant, the ovarian tissue is transplanted back." So far the Cornell group has generated embryos from the frozen ovarian tissue but no pregnancies. "When there's no time left to stimulate the ovaries before chemo or surgery starts," says Oktay, "this new, still-experimental technique may be worth considering."

Pregnancy after Cancer Treatment

Fertility-preserving surgery and assisted reproduction certainly increase the potential for a biological family of one's own. But it can be difficult for a cancer patient to decide when or how to have a child. "Anyone who has had cancer always worries about when it is safe to try to get pregnant," says Westphal, "especially because if cancer were to recur when a woman is pregnant, making decisions about her treatment could become far more difficult."

For women with breast cancer, the association between risk of recurrence and pregnancy, which increases estrogen levels, remains unresolved. "The research at the present time is limited," says Partridge of Dana-Farber. "And it is flawed by certain biases, especially the *healthy mother bias*, which means that those most likely to do well go on to get pregnant, both because they physically can and because they may be more likely to be counseled that it's okay."

Yet Stanford's Lynn Westphal says the fact that we are having these discussions at all represents hope, and a paradigm shift in the cancer community at large. "It is a sign of the times that our treatments are getting better, allowing us to focus on survivorship issues like fertility after cancer. It is a huge movement in the field."